Pharmacy

289

THERAPEUTIC CYCLOSPORINE (CSA) MONITORING AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT): HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC) OR TDX?

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CsA level ranges for GVHD prophylaxis have been developed based on HPLC which estimates the parent (active) drug, but is cumbersome. TDx, a monoclonal antibody assay for CsA, is quicker but also measures some of the metabolites which are biologically inactive. An internal feasibility study was done to consider switching from HPLC to TDx. 72 blood samples from 6 HSCT recipients (5-19 each) submitted for routine HPLC testing were also subjected to TDx. There was no charge for TDx. Only HPLC results were available for clinical use. There was strong correlation between HPLC and TDx results for the whole group ($r = 0.92$; $P = 10^{-29}$), and for each patient individually ($r = 0.75$-0.99; $P = 0.002$ to 10^{-8}). The regression model was: HPLC = 0.55TDx-14.38. The mean (SD) TDx and HPLC levels were 675 (251) and 359 (149). The TDx/HPLC ratio was 1.34-2.67 (median 1.92). There was no relationship between the TDx/HPLC ratio and time from starting CsA, BUN, creatinine, bilirubin, albumin, ALT, AST, or alkaline phosphatase. When HPLC was calculated (c-HPLC) from TDx using a simplified bedside formula (c-HPLC = TDx/1.9), the difference between c-HPLC and actual HPLC (a-HPLC) was -29% to +41% (median +1%). 51% of the paired readings differed by >10%, and 14% by >20%. Assuming 200-400 as the therapeutic range, 31 a-HPLC readings required dose adjustment (8 increase, 23 decrease) compared with 28 c-HPLC (6 increase, 22 decrease). Actions (increase, decrease, or no change) suggested by a-HPLC and c-HPLC were concordant in 59 cases and discordant in 13 (18%). Discordance was defined as "potentially critical" (change suggested by a-HPLC but no change suggested by c-HPLC) in 8 instances, and "not critical" in 5 (change suggested by c-HPLC and no change suggested by a-HPLC; where a % change in c-HPLC towards normal when applied to a-HPLC would not have resulted in a-HPLC going out of the therapeutic range). Our data show that while there is considerable intra-patient variability in the TDx/HPLC ratio, the correlation between HPLC and TDx is very strong. TDx can be substituted for HPLC with a sutiable modification in the therapetic range (380-760 here). Using TDx in our practice is unlikely to result in the CsA level deviating from the therapeutic range most of the time; including in patients with severe liver and/or kidney dysfunction. It must be emphasized that in practice, therapeutic CsA monitoring usually plays a secondary role to the clinical picture (evidence of drug toxicity and GVHD).

290

TACROLIMUS (FK-506) AND MYCOPHENOLATE MOFETIL (MMF) GVHD PROPHYLAXIS IN PEDIATRIC ALLOGENEIC SCT (ALLOSCT) RECIPIENTS: ALTERED MMF PHARMACOKINETICS (PK) ASSOCIATED WITH ACUTE (A)GVHD

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FK-506/MMF is an effective salvage therapy for steroid-refractory chronic (C)GVHD (Mookerjee et al, BMT:24:517, 1999) and prophylaxis of A and CGVHD following nonmyeloablative and fully ablative conditioning in adults (Rini et al, JCO, 2002; Pavletic et al Blood, 2002; McSweeney et al, Blood, 2002). We investigated the safety and efficacy of a FK-506/MMF regimen for AGVHD prophylaxis in 47 patients (mean age 8.5 yrs [range 0.5-21 yrs]; 31 M, 16 F) undergoing 51 AlloSCTs for hematologic malignancies (n = 27), non-malignant disorders (n = 16), and neuroblastoma (n = 4). FK-506 was given 0.03 mg/kg/day continuous IV on Day -1 or 1st day of conditioning plus MMF 15 mg/kg/dose PO/IV BID starting Day +1. Doses were adjusted to maintain trough steady state concentrations within reference ranges of 5-20 ng/mL for FK-506 and 1-3.5 mcg/mL for mycophenoleic acid (MPA). HLA typing was low resolution for A, B and C and high resolution for DR alleles. Stem cell sources: 6/6 UCB (n = 4), 6/6 related (R) UCB (n = 1), 5/6 UCB (mismatch: class I [n = 8]), 4/6 UCB (mismatch: class I [n = 9], class II [n = 2], class I/II [n = 8]), 6/6 RBM (n = 6), 5/6 RBM (mismatch: class I [n = 1], class II [n = 1]), 6/6 RPBSCT (n = 10), 10/10 unrelated PBSCT (n = 1). Conditioning types were: reduced intensity (n = 25) and myeloablative (n = 26). Mean time to ANC ≥500/mm^3 x 2 days (n = 42) was 13.8 ± 1.7 days and 25.9 ± 17 days following RPBSCT/BM and UCB, respectively. Mean time to platelet engraftment (≥20K/mm^3 x 7 days) was 14.7 ± 6 days for RPBSCT/BM and 61.3 ± 57.7 days for UCB recipients. Mean follow up was 324 days (17-989). Among 39 evaluable transplants, Kaplan-Meier probability of developing ≥grade II AGVHD was 43.7 ± 8% (36.1 ± 10.4% for UCB and 56.2 ± 12.4% for MFD recipients) and CGVHD was 38 ± 20% at 18 mos. FK-506/MMF were well tolerated, with 1 episode of grade IV hyperglycemia and 3 episodes of grade III-IV neurotoxicity. Probability of 1-year OS was 56 ± 12%. Probability of developing ≥grade II AGVHD was 36.2 ± 13.1% for patients who achieved MPA trough ≥1 mcg/mL prior to Day +30 vs 85.7 ± 13.2% for those who did not ($p = 0.017$). These results suggest that FK506/MMF is a safe and effective GVHD prophylaxis regimen following related and unrelated AlloSCT in children. Subtherapeutic MPA trough concentrations are associated with a significantly increased incidence of ≥grade II AGVHD. Further MMF pharmacokinetic/pharmacodynamic studies are ongoing in pediatric AlloSCT recipients to define the optimal dose and schedule of MMF.

291

SHOULD SERUM VORICONAZOLE (VORI) LEVELS BE MONITORED IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) RECIPIENTS?

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Vori has significant activity against *Candida* and *Aspergillus*. It is metabolized by the hepatic cytochrome P450 enzymes 2C19, 2C9 and 3A4. CYP2C19, which plays a significant role in the metabolism, exhibits significant genetic polymorphism. As a result, some patients metabolize Vori poorly. The clinical significance of this and resultant possible increases in Vori levels is unknown, and the utility of monitoring Vori levels is unclear. We monitored steady-state trough serum Vori levels in 22 allogeneic HSCT recipients using a new HPLC assay (Pennick et al. Antimicrob Agents Chemother 2003;47:2348-50). All had received non-myeloablative conditioning with 100 mg/m^2 melphalan (+50 mg/kg cyclophosphamide if not prior autograft). GVHD prophylaxis comprised cyclosporine/tacrolimus with mycophenolate mofetil. Vori was started at 200 mg BID PO in 20 patients, and 400 mg BID for a day followed by 200 mg BID in 2. One had aspergillosis, and the rest were receiving Vori prophylactically or empirically. Patients had drug levels checked once (n = 12), twice (n = 8), or ≥3 times (n = 2); 5 days to 9 months (median 10 days) after starting Vori or dose modification. The intention was to achieve a level greater than 0.5-1.0 μg/mL corresponding to the *in vitro* MIC_{90} of Vori for *Aspergillus* spp. The 22 baseline levels ranged from 0.2 to 6.8 μg/mL (median 1.1). Overall, the 36 levels were 0.2-6.8 (median 1.7); with 5 levels <0.5. An increase in the dose to 300 mg twice daily in 3 patients (2 with levels <0.5 and 1 with a level of 1.0 in the presence of aspergillosis) increased the level 6- to 8-fold. There was no significant correlation between Vori levels and serum creatinine, bilirubin, and ALT. Vori levels correlated with alkaline